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| EXAMINER | |
|---|---|
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/527,950 | TULLY ET AL. | |
| | Examiner | Art Unit | |
| | Aditi Dutt | 1649 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-4,6-10.12-15,17-22,24-25* is/are pending in the application.

4a) Of the above claim(s) *17,18 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-10,12-15,19-22,24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 26 October 2009 has been entered.

### *Status of Claims*

2. The amendment filed on 26 October 2009 has been entered into the record and has been fully considered. Claims 1, 6-7, 12 and 19 have been amended. Although Applicant stated that claim 24 is presently amended (Applicant's Remarks dated 10/26/09, page 11, line 4), the claim reads "previously presented" with no amendments.

3. Claims 1-4, 6-10, 12-15, 19-22 and 24, drawn to a method of identifying candidate compounds for enhancing CREB pathway function and assessing the effect on CREB-dependent gene expression, are under consideration in the instant application.

***Response to Amendment***
***Withdrawn objections and/or rejections***

4. Upon consideration of the Applicant's persuasive arguments explaining the differences between the claimed invention and the prior art references, particularly the primary reference by Sheriff et al., accompanied with appropriate claim amendments to clarify the method steps, all claim rejections under 35 USC 103(a), have been withdrawn.

***New Objections/Rejections***

***Claim Objection***

5. Claim 24 is objected to because of the following informalities: Claim 24 recites "the method of claim 19 wherein steps a) to e) are repeated …..selected in step e). The step numbers of claim 24 do not incorporate the amendments of claim 19.

Appropriate correction is required.

***Claim Rejections - 35 USC § 112-Second paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-4, 6-10, 12-15, 19-22 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly

point out and distinctly claim the subject matter which applicant regards as the invention.

7. The claims are vague and unclear for reciting the limitation "indicator activity is increased". Also claim 19(q)(i) recites “increased....gene expression". The instant specification teaches statistically significant increase in indicator activity (see para 0007) or statistically significant increased gene expression (see para 0008). It is not clear whether the limitation “increased” in the claims reads on being statistically significant. For purposes of applying rejection over prior art, the limitation will be interpreted as broadly reading on any increase (irrespective of statistical significance).

***Claim Rejections - 35 USC § 112-Scope of Enablement***

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 7-10, 12-15, 19-22 and 24, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying a candidate compound for enhancing cyclic AMP response element binding protein (CREB) pathway function by contacting host cells/cells of neural origin with a test compound and forskolin, wherein the indicator activity/CREB dependent gene expression

in cells treated with forskolin and test compound is significantly increased versus that observed with cells plus forskolin alone, does not reasonably provide enablement for the identification of a candidate compound following the same steps using any CREB function stimulating agent resulting in any difference in CREB dependent gene expression between the groups as stated above (see claims 7-10, 12-15). The specification is also not enabled for a non-significant increase in CREB dependent gene expression between the groups as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

10. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, include the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

11. The claims are directed to a method of identifying candidate compounds for enhancing CREB pathway function, (i) by contacting host cells comprising an indicator gene linked to a CRE promoter with a test compound and CREB function stimulating agent (forskolin); (ii)

determining the indicator activity and comparing the same in the above cells versus control cells contacted with the CREB function stimulating agent but not the test agent; (iii) selecting the test compound if the indicator activity in cells treated with CREB function stimulating agent but not the test agent is increased relative to the above control cells; (iv) selecting the test compound if the indicator activity in control cells not treated with the CREB function stimulating agent but with the test agent is not significantly different from the activity elicited by control cells neither treated with the test agent nor with the CREB function stimulating agent; (v) repeating the above steps with a range of concentrations of the test agent; wherein the indicator gene is luciferase. The claims further recite identifying and confirming the candidate compound by assessing the effect on CREB-dependent gene expression by contacting cells of neural origin (hippocampal neurons) with the candidate compound and CREB function stimulating agent, assessing and comparing the difference in the endogenous CREB dependent gene expression in the above cells versus that observed in control cells that have been contacted with the CREB function stimulating agent but not with the candidate compound, wherein the compound is selected if the gene expression in the above treated cells is different or significantly increased relative to control groups matching treatment criteria as in (ii), (iii) and (iv).

12. The specification of the instant application teaches high throughput cell-based assays comprising primary, secondary and tertiary screens for

identifying cognitive enhancers that act by increasing CREB pathway function, wherein the cognitive enhancers do not have any effect on CREB pathway function alone, however, enhance the activity in combination with a CREB stimulating agent (page 2, lines 8-12). The instant specification lists a vast array of CREB stimulating agents comprising drugs, chemical compounds, co-factors, saccharides, genes, ..... etc (page 17, lines 18-31; page 18, lines 1-5). The specification further teaches that the CREB dependent gene expression in cells treated with a CREB function stimulating agent (forskolin) and a test compound is "statistically significantly increased relative to the endogenous CREB-dependent gene expression in the control cells", wherein the control cells are represented by cells treated with forskolin alone (para 0008). However, the specification does not teach that the observation of any difference (an increase or a decrease) (emphasis added) in CREB dependent gene expression would indicate that the compounds are CREB pathway function enhancers as claimed. Likewise, the specification does not enable a skilled artisan to predictably confirm test compounds as CREB activators, even if the increase in CREB dependent gene expression is not statistically significant. Furthermore, the specification does not teach any methods or working examples to indicate that all CREB function stimulating agents will effectively function at a suboptimal dose with all test agents, to enhance CREB pathway function. Undue experimentation would be required of a skilled artisan to determine such.

13. The art teaches that CREB is regulated by multiple factors producing “diverse stimuli” that “can result in divergent cell fates” (Pugazhenthi et al. J Biol Chem 274: 2829-2837, 1999; Discussion, page 2834-2835, para 2-3). The art also demonstrates that different CREB function stimulating agents function differently either alone, and/or in combination with test agents, that would complicate the process of efficient screening. For example, NPY (neuropeptide Y) augments forskolin stimulated luciferase activity, but does not affect the thapsigargin (a modulator of intracellular calcium concentration and a CREB function stimulating agent as described in the instant specification – page 17, lines 26-27) induced activity significantly (Sheriff et al. Reg Pept 75-76: 309-318, 1998; abstract; Figure 5). Additionally, thapsigargin depletes intracellular calcium stores, thereby preventing NPY which acts on the reporter gene via intracellular calcium to exert an enhanced effect. In addition, the instant specification teaches that the "suboptimal dose of CREB stimulating agent is determined empirically and will vary depending upon a variety of factors, including the pharmacodynamic characteristics of the particular CREB function stimulating agent and the particular cells to be contacted” (page 20, lines 1-4), thereby implying the potential variability and unpredictability in obtaining successful results. In the absence of guidance regarding the use of any CREB function stimulating agent at a suboptimal dose, resulting in any difference in CREB dependent gene expression, for identifying a candidate compound that will enhance CREB

function with a reasonable amount of success and predictability, undue experimentation would be required of a skilled artisan. The specification must provide such guidance commensurate in scope with the claims. The specification's general discussion of a broad range of CREB stimulating agents and the breadth of “a difference” in the CREB dependent gene expression in cells with or without test compound, constitute an invitation to experiment by trial and error.

14. Due to the large quantity of experimentation necessary to identify a candidate compound for enhancing CREB pathway function by using any CREB function stimulating agent at a suboptimal dose and obtaining any difference in the CREB dependent gene expression, the lack of direction/guidance presented in the specification; the absence of working examples directed to same; the complex nature of the invention; and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

15. Claims 1-4, 6-10, 12-15, 19-22 and 24 are rejected under 35 U.S.C. 102(b) as clearly anticipated by Scott et al., (2002).

16. The claims are directed to a method of identifying candidate compounds for enhancing CREB pathway function, (i) by contacting host cells comprising an indicator gene linked to a CRE promoter with a test compound and CREB function stimulating agent (forskolin); (ii) determining the indicator activity and comparing the same in the above cells versus control cells contacted with the CREB function stimulating agent alone; (iii) selecting the test compound if the indicator activity in cells treated with CREB function stimulating agent and test compound is increased relative to the above control cells; (iv) selecting the test compound if the indicator activity in control cells treated with test agent is not significantly different from the activity elicited by control cells not treated with any agent; (v) repeating the above steps with a range of concentrations of the test agent; wherein the host cells are neuroblastoma cell, and the indicator gene is luciferase (claims 1, 3-4, 6). The claims further recite identifying and confirming the candidate compound by assessing the effect on CREB-dependent gene expression by contacting cells of neural origin (hippocampal neurons) with the candidate compound and CREB function stimulating agent, assessing and comparing the difference in the endogenous CREB dependent gene expression in the above cells versus that observed in control cells that have been contacted

with the CREB function stimulating agent only, wherein the compound is selected if the gene expression in the above treated cells is different or significantly increased relative to control groups matching treatment criteria as in (ii), (iii) and (iv) (claims 7, 9, 10, 12, 14-15, 19-22, 24). Lastly, the claims recite that the host cells or the cells of neural origin are contacted with the test/candidate compound prior to contact with the CREB function stimulating agent (claims 2, 8, 13).

17. Scott et al. teach cell-based high throughput screening assays using a plurality of compounds for the discovery of pharmaceutical therapeutics for treating cognitive dysfunction, wherein the compounds have an effect on CREB function. The reference teaches the transfection of host cells or neuroblastoma cells with a reporter construct having a luciferase gene under the control of a CRE promoter, wherein the CREB function is monitored using fluorescence signals. The cells are pre-incubated in the presence of the test compound, thereafter are contacted with a suboptimal dose of forskolin, followed by determining the luciferase reporter activity in the various groups. Scott et al. demonstrate that only test compounds that produce a greater than or equal to 100% increase or a significant increase in luciferase signal over control cells stimulated with forskolin alone, and which do not enhance CREB function on their own, are selected for the next round of screening. The reference also teaches that the compounds are tested at four different concentrations. The test compounds are further confirmed by contacting with rat primary

hippocampal neurons to assess the effects of the compounds on CREB dependent gene expression. Scott et al. demonstrate that the selected test compounds elicit a gene expression data profile that is comparable in potency to the luciferase indicator activity (abstract; page 172, col 2, para 4, 6; page 173, col 1, para 1-4). Because Scott et al. teach all method steps of the screening assay as claimed, the reference anticipates the instant invention.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the

examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 1-4, 6-10, 12-15, 19-22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ying et al. (1997), in view of Scott et al., (2002).

20. Ying et al. teach that host cells (Calu-6 or human lung cancer cells) were transiently transfected using plasmids comprising the HREN promoter having the consensus CRE sequence (e.g. 900L, 900CRE, etc.) (Table 1; Figure 1), luciferase indicator gene, along with expression vector encoding the CREB-1 transcription factor (interpreted as the CREB pathway enhancing molecule) (abstract) and contacted with forskolin (Materials and Methods, page 2413, col 2, para 2). The reference further teaches that the luciferase activity elicited by cells transfected with reporter constructs 900L or 900CRE, and contacted with CREB expression vector along with forskolin is significantly increased with respect to cells without the CREB expression vector. Additionally, the cells not treated with forskolin and CREB expression vector are not significantly different than cells in contact with CREB expression vector alone (Figure 6A). Please note that the CREB vector can function as a CREB analog to enhance CREB function, therefore is interpreted as having the same properties of the claimed test compounds.

21. Ying et al. do not teach the determination of CREB dependent gene expression using neural cells, or screening a plurality of compounds that would enhance CREB function.

22. The teachings of Scott et al. are set forth above.

23. It would have been, therefore, obvious to the person of ordinary skill in the art at the time the claimed invention was made to modify the method of determining CREB function enhancement in the presence of forskolin as taught by Ying et al. by proceeding to secondary and tertiary screening of such compounds or molecules for determining their effects on CREB dependent gene expression in neural cells as taught by Scott et al. The person of ordinary skill in the art would have been motivated to perform further screening of compounds based on the teachings of Ying et al. that conform with the two basic guidelines for drug-discovery in view of Scott et al., i.e. “active compounds are sought that do not enhance CREB function on their own but rather after co-stimulation with forskolin” (Scott et al. page 172, col 2, para 4). Additionally because of the involvement of CREB pathway in multiple biological and cognitive functions as stated above, the skilled person would be motivated to screen for multiple compounds. The person of ordinary skill in the art would have expected success because the method assessing in vitro activity of regulatory peptides as a part of screening for candidate compounds for drug development for example was being experimented and performed in the scientific and medical community, at the time the invention was made.

Therefore, the claimed invention as a whole was clearly *prima facie* obvious over the prior art.

24. Claims 1-4, 6-10, 12-15, 19-22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barad et al. (1998), in view of Scott et al., (2002).

25. Barad et al. teach a method of elevating cAMP concentrations, using hippocampal slices from mice, that were incubated with increasing range of 4 concentrations of the phosphodiesterase type IV inhibitor, rolipram (0, 0.03, 0.3 and 3 μM) in the presence or absence of the adenylyl cyclase activator forskolin (abstract, page 15021). The reference also demonstrates that cAMP levels at lower concentrations of rolipram (up to 0.3 uM) were not significantly different from the basal level (without rolipram and forskolin) (page 15021, 'results' para 1, Figure 1). Furthermore, the results demonstrate that the endogenous cAMP levels in cells contacted with rolipram and forskolin are significantly increased relative to the levels in the control group treated with forskolin but not rolipram. It is noted that forskolin is an adenylyl cyclase activator as stated above, which would inherently increase endogenous cAMP concentrations via increased adenylyl cyclase expression as evidenced by Insel et al (Cell Mol Neurobiol 23: 305-314, 2003, abstract). It is also well known that adenylyl cyclase is a positive effector of CREB, inducing CREB dependent gene expression.

26. Barad et al. do not teach the determination of CREB dependent gene expression using hippocampal cells.

27. It would have also been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of elevating cAMP levels from hippocampal slices as taught by Barad et al., by enhancing CREB dependent gene expression in hippocampal neurons as taught by Scott et al. The person of ordinary skill in the art would have been motivated to substitute the use of hippocampal slices with hippocampal neurons, because neurons are individual cells that would elicit the CREB dependent gene expression in a cell specific manner. The person of ordinary skill in the art would have been further motivated to proceed with screening of compounds based on the teachings of Barad et al. that conform with the two basic guidelines for drug-discovery in view of Scott et al., i.e. “active compounds are sought that do not enhance CREB function non their own but rather after co-stimulation with forskolin” (Scott et al. page 172, col 2, para 4). Additionally because of the involvement of CREB pathway in multiple biological and cognitive functions as stated above, the skilled person would be motivated to screen for multiple compounds. The person of ordinary skill would make that modification with a reasonable expectation of success, because gene expression studies using individual neurons were well established at the time of filing of the instant invention.

28. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

## ***Conclusion***

29. No claims are allowed.

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

31. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery Stucker, can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

32. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
30 December 2009

/Jeffrey Stucker/

Supervisory Patent Examiner, Art Unit 1649